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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/03/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,285	LIU ET AL.	
	Examin r	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23, 27, 28, 32-35, and 61-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27,28,32-35,67 and 68* is/are allowed.

6)☐ Claim(s) *23, 61-66, and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response, on June 24, 2003, Paper No. 16, to the first Office Action on the Merits of this case is acknowledged. It is acknowledged that applicants have amended Claims 28, 32, and 33, cancelled Claims 1-22, 24-26, 29-31, and 36-60, added new Claims 61-63, and reinstated Claims 24, 25, 26, 29, 30, and 31 as new Claims 64, 65, 66, 67, 68, and 69, respectively. Claims 23, 27, 28, 32-35, and 61-65 are pending. Claims 23, 27, 28, 32-35 are hereby reconsidered and new Claims 61-65 are considered.

Oath/Declaration

Objection to the Oath/Declaration is maintained. Receipt of the Supplemental Declaration filed June 24, 2003 is acknowledged. But, said declaration still does not identify the date of execution for the signature of Ram Sasisekharan. A new and dated signature may be provided on a supplemental oath or declaration.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of Claim 23 under 35 U.S.C. 112, second paragraph, as being indefinite is maintained. The rejection was based on the fact that Claim 23 has two possible interpretations: that the recited composition comprises, heparinase III, a targeting molecule, and a carrier (three independent substances) or that the recited composition comprises a fusion protein of heparinase III linked to a targeting molecule and a carrier (two independent substances). Applicants acknowledged that Claim 23 encompasses said two interpretations and asserts that, although the claim does encompass both interpretations, this does not mean that the claim is vague and

indefinite. Applicants further argue that a person of ordinary skill in the art would be able to recognize compositions that contain these three components, regardless of whether they are linked or not. These arguments are not found to be persuasive. Claim 23 is confusing in reciting a composition comprising heparinase III and a targeting molecule, suggesting these are two separate entities because the specification, applicant's arguments, and the function of all targeting molecules suggest the two entities are linked. Therefore, rejection of Claim 23 under 35 U.S.C. 112, second paragraph, as being indefinite is maintained. New Claims 64-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons.

NEW ISSUES

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62-65, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claims 62 and 63, the phrase "conservative substitutions" is indefinite. It is acknowledged that the specification presents an explanation of conservative substitutions on pages 12-13. However, said explanation is, in part, indefinite in the recitation of "amino acid analogs and variants". A person of ordinary skill in the art would not be apprized of how said unidentified amino acid analogs and variants could be used for "conservative substitutions" of

any of the amino acid residues in heparinase III. Thus, Claims 62 and 63 are rejected under 35 U.S.C. 112, second paragraph.

Claim 62 is confusing in reciting "heparinase III of Claim 32 and additional limitations excluded from the scope of Claim 32.

Claim 63 is confusing in reciting "heparinase III of Claim 33 and additional limitations excluded from the scope of Claim 32.

In Claim 64 the term "modified" renders the claim indefinite. It is not clear whether the "modified heparinase III" is mutated within the polypeptide sequence of heparinase III or whether the "modified heparinase III" has the wild-type sequence of heparinase III and is fused to a targeting molecule. Thus, Claim 64 is rejected under 35 U.S.C. 112, second paragraph.

In Claim 65 the term "native" renders the claim indefinite. It is not clear whether the "native heparinase III" is simply the wild-type heparinase III or the wild-type heparinase III linked to a targeting molecule. Thus, Claim 65 is rejected under 35 U.S.C. 112, second paragraph.

Claim 69 is confusion in reciting dependence from a cancelled claim. It is not clear whether Claim 69 is meant to depend from Claim 28 or Claim 29. Clarification is required.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These

factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 23, 27, 64, and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide set forth by SEQ ID NO: 2 as well as said polypeptide having His36Ala, His105Ala, His110Ala, His139Ala, His152Ala, His225Ala, His234Ala, His241Ala, His424Ala, His469Ala, or His539Ala mutation (Table 2) and said polypeptide having at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine, does not reasonably provide enablement for a composition comprising any native or modified protein having heparinase III activity or any HLGAG fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 23 and 27 are so broad as to encompass a composition comprising any protein having heparinase III activity or any protein having the activity of a HLGAG fragment. Claim 64 is so broad as to encompass a composition comprising any modified protein having heparinase III activity. Claim 65 is so broad as to encompass a composition comprising any

native protein having heparinase III activity. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired heparinase III activity or HLGAG fragment activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 23 and 27, which encompasses all compositions comprising any protein having heparinase III activity or any HLGAG fragment. The specification does not support the broad scope of Claim 64, which encompasses a composition comprising any modified protein having heparinase III activity. The specification does not support the broad scope of Claim 65, which encompasses a composition

comprising any native protein having heparinase III activity. The specification does not support the broad scope of Claims 23, 27, 64, and 65 because the specification does not establish: (A) the identity of all proteins having heparinase III activity and or the activity of a HLGAG fragment; (B) regions of said proteins' structures which may be modified without effecting their activities; (C) the general tolerance of the activities of heparinase III and HLGAG fragments to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of proteins having heparinase III activity or the activity of a HLGAG fragment, and proteins having an enormous number of amino acid modifications thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 23 and 64-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising heparinase III linked to a targeting molecule in a pharmaceutically acceptable carrier, it does not reasonably provide

enablement for a composition comprising heparinase III and a targeting molecule in a pharmaceutically acceptable carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 23 is so broad as to encompass any composition comprising heparinase III and a targeting molecule in a pharmaceutically acceptable carrier, wherein the targeting molecule is not linked to heparinase III but still targets heparinase III to a tumor. The scope of this claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of compositions broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, including interaction with other proteins, predictability of which targeting molecules can be used to obtain the desired targeting of heparinase III when the targeting molecule and heparinase III are not linked, requires a knowledge of and guidance with regard to targeting molecules that are useful for said application and which amino acids in said targeting molecules' sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the targeting molecule's structure relates to its function. The specification fails to describe any targeting molecules that can be used for targeting heparinase III when not linked to heparinase III.

While recombinant and mutagenesis techniques as well as screening techniques to assess targeting of heparinase III to a tumor are known, it is not routine in the art to screen numerous targeting molecules. It is also not routine in the art to screen for multiple substitutions or multiple modifications of potential targeting molecules, as encompassed by the instant claims,

and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given targeting protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claim 23 which, encompasses any composition comprising heparinase III and a targeting molecule in a pharmaceutically acceptable carrier, wherein the targeting molecule is not linked to heparinase III but targets heparinase III to a tumor. The specification does not support the broad scope of Claim 23 because the specification does not establish: (A) any targeting molecules that can target heparinase III to a tumor when not linked to heparinase III; (B) regions of any targeting molecule's structure which may be modified to enhance the ability of the targeting molecule to target heparinase III to a tumor when not linked to heparinase III; (C) regions of any targeting molecule's structure which may be modified without effecting the targeting molecule's ability to target heparinase III to a tumor when not linked to heparinase III; (D) the general tolerance of the ability of any targeting to target heparinase III to a tumor when not linked to heparinase III to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (F) the specification provides no guidance as to which of the essentially infinite possible choices is likely to be successful.

Since Claims 64-66 are dependent on Claim 23, they are rejected under 35 U.S.C. 112 first paragraph due to lack of enablement for the same reasons discussed above.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of compositions comprising heparinase III and a targeting molecule in a pharmaceutically acceptable carrier, wherein the targeting molecule is not linked to heparinase III but still targets heparinase III to a tumor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of targeting molecules having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 61-63 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the polypeptide set forth by SEQ ID NO: 2 as well as said polypeptide having His36Ala, His105Ala, His110Ala, His139Ala, His152Ala, His225Ala, His234Ala, His241Ala, His424Ala, His469Ala, or His539Ala mutation (Table 2) and said polypeptide having at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine; however, the specification is not enabling for any heparinase III wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and having any number of additional conservative substitutions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claim 61 is so broad as to encompass any heparinase III derived from SEQ ID

NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function. Claim 62 is so broad as to encompass any modified heparinase III derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function, wherein the modified heparinase III has a product profile that is modified by 10%, compared to the native product profile. Claim 63 is so broad as to encompass any modified heparinase III derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function, wherein the modified heparinase III has a k_{cat} value that is at least 10% different than the k_{cat} value for a native heparinase III. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired heparinase III activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO: 2 and modified proteins

derived from said SEQ ID NO: 2 with a His36Ala, His105Ala, His110Ala, His139Ala, His152Ala, His225Ala, His234Ala, His241Ala, His424Ala, His469Ala, or His539Ala mutation and polypeptides derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claim 61 which, encompasses any heparinase III derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function. The specification does not support the broad scope of Claim 62 which, encompasses any modified heparinase III derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function, wherein the modified heparinase III has a product profile that is modified by 10%, compared to the native product

profile. The specification does not support the broad scope of Claim 63 which, encompasses any modified heparinase III derived from SEQ ID NO: 2 wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and further comprising substitution within residues non-essential to enzymatic function, wherein the modified heparinase III has a k_{cat} value that is at least 10% different than the k_{cat} value for a native heparinase III. The specification does not support the broad scope of Claims 61-63 because, the specification does not establish: (A) regions of the structure of the protein set forth by SEQ ID NO: 2 which may be modified without effecting the activity of heparinase III; (B) the general tolerance of the activity of heparinase III to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; (D) specific substrates to be used to compare product profiles; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of heparinase III molecules, derived from the protein set forth by SEQ ID NO: 2, with an enormous number of amino acid modifications of said protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and

improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants assert the following to argue that Claims 23 and 61-66 are enabled by the specification. That, the number of species provided is sufficient. That, the claimed substitutions are predictable. That, screening for multiple modifications is routine in the art. That, the specification, working examples, and level of skill in the art provide sufficient guidance for one of ordinary skill to identify, make, test and use the recited modified heparinase III molecules. These arguments are not found to be persuasive for the following reasons.

Regarding the number of species provided being sufficient, Table II provides information on the activity of 13 species of heparinase III wherein one of the recited histidine residues of SEQ ID NO: 2 is replaced with an alanine. Said species do not provide information on the activity of proteins derived from SEQ ID NO: 2, having: (i) replacement of any one said histidine residues with alanine and replacement of any other residue with a "conservative substitution", (ii) replacement of any one said histidine residues with serine, threonine, tyrosine, or lysine and replacement of any other residue with a "conservative substitution", (iii) replacement of more than one said histidine residues with alanine and replacement of any other residue with a "conservative substitution", (iv) replacement of more than one said histidine residues with any of alanine, serine, threonine, tyrosine, or lysine and replacement of any other residue with a "conservative substitution". The identity of which, if any, of the above variants have the desired activity is not enabled by the species disclosed in Table II.

Regarding the predictability of the claimed substitutions, the effect for replacement of any amino acid residue can be unpredictable. Wisehart et al, 1995 teach that a single mutation of

a Gly residue to a Cys residue ($G^{120}C$) converts a phosphotyrosine binding-domain into a dual-specificity phosphatase (Fig 4). While, as taught by Witkowski et al, 1999, a single mutation of a Cys residue for a Gln residue ($C^{161}Q$) converts a β-ketoacyl synthase to a malonyl decarboxylase (Fig 3). Thus, the effects of mutation on a protein's activity are unpredictable.

Regarding screening for multiple modifications as routine in the art, although screening techniques are known, screening the number of variants encompassed by the claims represents undue experimentation. Neither the specification, the teachings of the art, nor the skill of a person of ordinary skill in the art are sufficient to enable such a person to identify, without undue experimentation, those variants that are likely to be useful for the recited utility. For these reasons, applicants' arguments are not found to be persuasive.

Claims 23, 27, and 64-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These Claims 23, 27, 64, and 65 are directed to compositions comprising a genus of protein molecules from any source having heparinase III activity or the activity of a HLGAG fragment. The specification teaches the structure of only a single representative species of such protein molecules having heparinase III activity and no representative species of molecules having the activity of a HLGAG fragment. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having heparinase III activity or the activity of a HLGAG fragment. Claims 23 and 64-66 are directed to a genus of compositions comprising any targeting molecule that can target heparinase III to a tumor when not linked to heparinase III.

The specification teaches the structure of no representative species of such targeting molecule. Claims 61-63 are directed to a genus of modified heparinase III derived from the protein set forth by SEQ ID NO: 2 and having substitution within residues non-essential to enzymatic function. These claims are also directed to a genus of modified heparinase III derived from the protein set forth by SEQ ID NO: 2 and having at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 substituted with alanine, serine, tyrosine, threonine, or lysine and further having substitution within residues non-essential to enzymatic function wherein the modified heparinase III has either (i) a modified product profile, using any substrate, that is at least 10% different from a native profile or (ii) a K_{cat} that is at least 10% different from a native K_{cat} using heparan sulfate as the substrate. The specification teaches the structure of only 13 representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having heparinase III activity. Given this lack of description of representative species encompassed by the genera of these claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants assert the following to argue that Claims 23 and 61-66 are sufficiently described by the specification. "The disclosure of the amino acid residues that play a role in the activity of heparinase III along with the number of described species is sufficient to demonstrate Applicants were in possession of the claimed invention." This argument is not found to be persuasive. Based on the effect of DEPC treatment and site-directed mutagenesis, the specification discloses that histidine residues are important in the activity of heparinase III.

However, the specification fails to disclose the role that any other amino acid residues play in the activity of heparinase III. As described above, Table II provides information on the activity of 13 species of heparinase III, wherein one of the recited histidine residues of SEQ ID NO: 2 is replaced with an alanine. Said species do not provide information on the specific structure and activity of proteins derived from SEQ ID NO: 2, having: (i) replacement of any one said histidine residues with alanine and replacement of any other residue with a "conservative substitution", (ii) replacement of any one said histidine residues with serine, threonine, tyrosine, or lysine and replacement of any other residue with a "conservative substitution", (iii) replacement of more than one said histidine residues with alanine and replacement of any other residue with a "conservative substitution", (iv) replacement of more than one said histidine residues with any of alanine, serine, threonine, tyrosine, or lysine and replacement of any other residue with a "conservative substitution". The structural identity of any of the above, having the desired utility, is not described by the species disclosed in Table II. Therefore, rejection of Claims 23 and 61-66 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

Allowable Subject Matter

Claims 28, 32-35, 67, and, 68 are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
Group 1600